AstraZeneca

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OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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Study Statistician	PPD	13 DEC 2019 Date
Epidemiologist	PPD	13 DEC 2019 Date

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Global Product Statistician PPD 17 DECEMBER 2019

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase/transaminase
AML	acute myeloid leukemia
AST	aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
BRCA	breast cancer susceptibility gene
CI	confidence interval
CM	concomitant medication
CR	complete response
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor deoxyribonucleic acid
CTCAE	Common Terminology Criteria for Adverse Events
CT-FI	chemotherapy-free interval
CTMS	clinical trial management system
DCO	data cut-off
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EQ-5D-5L	EuroQol five dimensions, five levels
EWB	emotional well-being
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	full analysis set
FWB	functional well-being
g*BRCA*	germline *BRCA*
g*BRCA*m	germline *BRCA* mutation (or mutated)
HGSOC	high-grade serous ovarian cancer
HRD	homologous recombination deficiency

Abbreviation or special term	Explanation
HRQoL	health-related quality of life
HRR	homologous recombination repair
IMP	Investigational medical product
KM	Kaplan-Meier
LD	longest diameter
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MSI	microsatellite instability
NA	not applicable
NTL	non-target lesion
OAE	other significant adverse event
OCS	ovarian cancer subscale
OS	overall survival
PFS	progression-free survival
PID	percentage intended dose
PR	partial response
PRO	patient-reported outcome
PSR	platinum sensitive relapsed
PT	preferred term
PWB	physical well-being
Q1	first quartile
Q3	third quartile
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or special term	Explanation
SAS	safety analysis set
s*BRCA*	somatic *BRCA*
SD	stable disease
SOC	System Organ Class
SWB	social/family well-being
TBL	total bilirubin
t*BRCA*	tumor *BRCA*
TDT	time to treatment discontinuation or death
TFST	time to first subsequent therapy or death
TL	target lesion
TOI	trial outcome index
TP53	tumor protein p53
ULN	upper limit of normal
VAS	visual analog scale
WHODrug	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Category: **Change refers to**	**Date**	**Description of change**	**In line with CSP?** **Y (version) / N / NA**	**Rationale**
Primary or secondary endpoints	09 December 2019	Redefined the HRD subgroups for the progression-free survival analysis (sections 3.3.3 and 4.2.5.3).	N	Based on evolving science and to generate olaparib efficacy data in sBRCAm population.
Primary or secondary endpoints	09 December 2019	Included a sensitivity analysis of the primary endpoint should there be a significant number of important protocol deviations reported (section 4.2.4.1).	NA	In order to assess impact of important protocol deviations on the primary endpoint.
Primary or secondary endpoints	09 December 2019	The interim analysis will also include the reporting of secondary endpoints (section 5).	NA	Updated based on regulatory feedback.
Derivation of primary or secondary endpoints	09 December 2019	Refined rules for patients with no evidence of disease at baseline (section 3.1.1) and updated the overall visit response definition of patients without any target lesions, non-target lesions at baseline and no new lesions post baseline (section 3.1.4; Table 4).	NA	In order to further clarify/correct derivations.

Derivation of primary or secondary endpoints	09 December 2019	Removed the derivation column (section 3.1.1; Table 2 and Table3).	NA	Removed as more appropriate for programming documentation.
Derivation of primary or secondary endpoints	09 December 2019	Updated the text for censoring for the endpoints time to first subsequent therapy or death and time to chemotherapy-free interval (sections 3.3.1 and 3.3.4).	NA	In order to further clarify censoring rules and ensure alignment across outcome variables.
Derivation of primary or secondary endpoints	09 December 2019	Added details to determine the last recorded date on which the patient was known to be alive (section 3.3.5).	NA	Undertaken to clarify where to censor patients who are alive and not in overall survival follow-up.
Data presentations	09 December 2019	Removed a sentence regarding the calculation of percentages with respect to missing values (section 4.1.2).	NA	Removed as this sentence is not applicable to all summary tables i.e. demographic summaries
Data presentations	09 December 2019	Tables presented by visit will also include study treatment discontinuation and follow-up after treatment discontinuation visits (sections 4.2.5.6 and 4.2.6.3). The time window definition for those visits has been added (section 4.1.5).	NA	Clarified in order to match with the requirements of the table shell.

Data presentations	09 December 2019	Patients ongoing/discontinuing study treatment categories included in the disposition summary table (section 4.2.1.1).	NA	In order to present the full list of disposition contents as per the table shell.
Data presentations	09 December 2019	Updated format of demographic and exposure summaries (section 4.2.1.3 and section 4.2.7.1).	NA	In order to match the requirements of the table shells and clarify derivations.
Data presentations	09 December 2019	Updated the format of event and censored categories (sections 4.2.5.1, 4.2.5.2, 4.2.5.4 and 4.2.5.5).	NA	Clarified in order to match the requirements of the table shell.
Data presentations	09 December 2019	Removed reference to the presentation of p-values (section 4.2.5.6).	NA	Since no statistical test is planned in this single arm study.
Other	09 December 2019	Updated the definition of the important protocol deviations (section 2.2).	NA	Updated the list to key criteria aligned with the AZ Oncology SAP guidance.
Other	09 December 2019	Included the definition of time on study (section 3.4.1.1).	NA	In order to clarify the derivation of this variable.
Other	09 December 2019	Updated the adverse events of special interest definition (section 3.4.2.1) and included summary tables for the common olaparib AEs (section 4.2.7.2)	NA	Updated to align with the standard project safety reporting rules/summaries.

Other	09 December 2019	Removed the reporting of PFS stratified into a range of molecular subgroups including microsatellite instability status and tumor mutation load score (sections 3.5.1 and 4.2.1.3).	N	Removed since such an analysis when split by such groups is unlikely to be meaningful i.e., microsatellite instability-H prevalence is very low in ovarian cancer; tumor mutation burden cut off of high vs low has not been established in ovarian cancer.
Other	09 December 2019	Included death as an event in time to PRO-deterioration (section 3.5.3)	NA	Included since death is standardly included as an event.
Other	09 December 2019	Added details of the components of the EQ-5D questionnaire (section 3.5.5)	NA	In order to aid understanding.
Other	09 December 2019	Imputation rules for missing stop dates updated (section 4.1.3).	NA	In order to provide more accurate data handling rules of missing stop dates compared to dose dates.
Other	09 December 2019	Clarified the text for the data cut-off definitions (section 4.1.4).	NA	In order to clarify the data cut-off principles for the interim and primary PFS analyses as well as OS.

Other	09 December 2019	Amended the percentages for relative dose intensity and percentage intended dose examples (section 8.1).	NA	In order to correct errors noted.

1. STUDY DETAILS

1.1 Study objectives

The study objectives are as follows:

Primary Objective:	**Outcome Measure:**
To determine the efficacy by progression-free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumors [RECIST v1.1]) of olaparib maintenance monotherapy in non-germline breast cancer susceptibility gene (*BRCA*) mutated (non-g*BRCA*m) platinum sensitive relapsed (PSR) ovarian cancer.	• PFS: Time from date of first dose until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression)
Secondary Objectives:	**Outcome Measures:**
To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of time to first subsequent therapy or death (TFST)	• TFST: Time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of first subsequent treatment
To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of time to treatment discontinuation or death (TDT)	• TDT: Time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation
To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance in non-g*BRCA*m PSR ovarian cancer according to tumor homologous recombination deficiency (HRD) status using the Myriad myChoice plus HRD test	• PFS in the following subgroups: 1. Somatic *BRCA* (s*BRCA*) mutated and HRD scar positive; 2. HRD scar positive, non-*BRCA* mutated; 3. HRD scar negative, non-*BRCA* mutated

To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of chemotherapy-free interval (CT-FI)	• CT-FI: Time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy
To determine the overall survival (OS) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy	• OS: Time from the date of first dose of olaparib to the date of death from any cause
To investigate the Health-related Quality of Life (HRQoL) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)	• Proportion of patients with any improvement from baseline in TOI score at any point during the treatment period • Proportion of patients with a 10 point deterioration from baseline in TOI score at any point during the treatment period
Safety Objective:	**Outcome Measures:**
To assess the safety and tolerability of olaparib maintenance monotherapy in patients with non-g*BRCA*m PSR ovarian cancer	• Adverse events (AEs)/serious adverse events (SAEs) • Collection of clinical chemistry/hematology parameters
Exploratory Objectives:	**Outcome Measures:**
To explore the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer patients stratified into a range of molecular sub-groups including mutations in Homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score.	• PFS by molecular measures of HRR and genomic instability
To explore the impact of tumor protein p53 (TP53) disruption status on both OS and PFS	• OS and PFS by TP53 disruption status

To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five levels (EQ-5D-5L)	• EQ-5D index score and the EQ-visual analog scale (VAS) score including the change from baseline for both scores
To explore the feasibility of reliably identifying mutations in homologous recombination genes from circulating tumor deoxyribonucleic acid (ctDNA) and to enable future diagnostic development	• Correlation between HRD status from tumor and ctDNA in matched patient samples

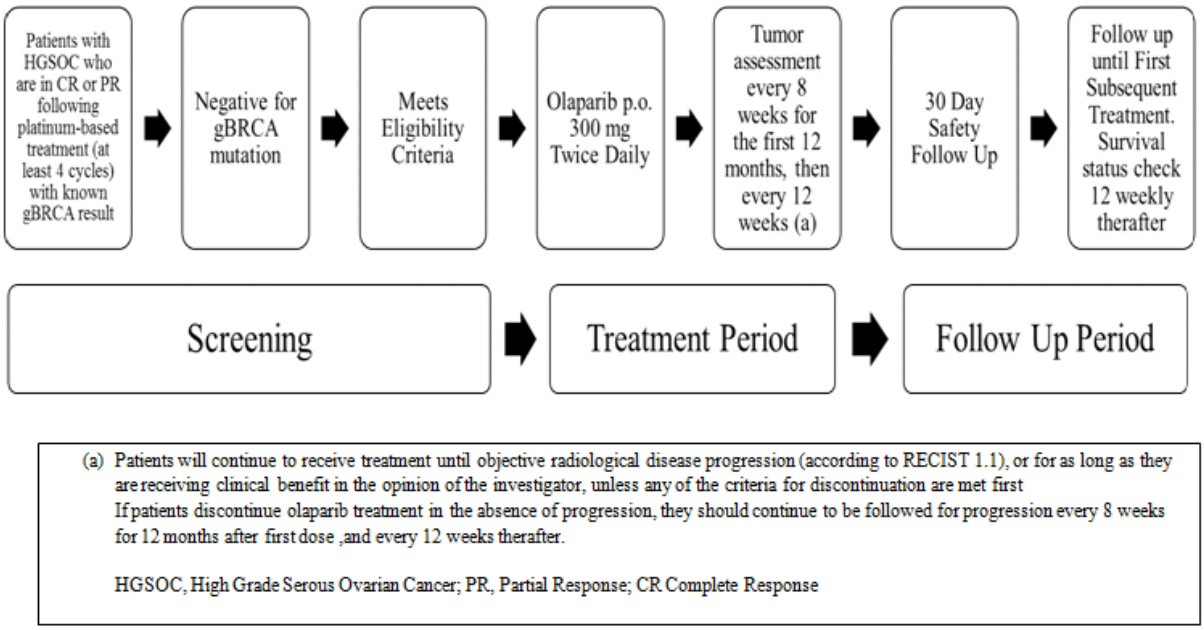
1.2 Study design

This is a Phase IIIb, single-arm, open-label multicenter study to assess the efficacy and safety of single-agent olaparib as a maintenance treatment in patients with relapsed high-grade serous ovarian cancer (HGSOC) (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer who do not have known deleterious or suspected deleterious germline *BRCA* mutations (g*BRCA*m) and who had responded following platinum-based chemotherapy.

Olaparib will be administered to all patients in this single-arm study (see Figure 1) at a starting dose of 300 mg twice daily. Dose reductions may be required in patients experiencing toxicities related to olaparib treatment or due to concomitant medication (CM).

Tumor assessments will be conducted every 8 weeks (± 7 days) in the first 12 months of follow-up, and thereafter every 12 weeks up to documented evidence of radiological disease progression in accordance to modified RECIST v1.1. The first tumor assessment visit will be conducted 8 weeks after the baseline visit (Day 57). Safety assessments will be conducted every 8 weeks (± 3 days) starting 4 weeks after the baseline visit (Day 29). Laboratory data and pregnancy tests are assessed at each visit. Eastern Cooperative Oncology Group (ECOG) will be performed at each tumor assessment visit. Safety-specific visits will cease after the first 12 months and safety tests will then be conducted at the tumor assessment visits only.

Figure 1: Protocol Schedule



(a) Patients will continue to receive treatment until objective radiological disease progression (according to RECIST 1.1), or for as long as they are receiving clinical benefit in the opinion of the investigator, unless any of the criteria for discontinuation are met first
If patients discontinue olaparib treatment in the absence of progression, they should continue to be followed for progression every 8 weeks for 12 months after first dose ,and every 12 weeks therafter.

HGSOC, High Grade Serous Ovarian Cancer; PR, Partial Response; CR Complete Response

1.3 Number of subjects

The primary endpoint is the investigator assessed PFS using modified RECIST v1.1.

A sample size of approximately 250 patients is proposed for this study in order to provide an adequate level of precision around the primary endpoint in the whole patient population. The primary analysis is planned at approximately 30 months after the first patient is enrolled, with an interim analysis after approximately 18 months. A supplementary analysis of OS will be performed when 135 OS events (~ 54% maturity) have been recorded, estimated to be approximately 36 months after the first patient is enrolled.

In published data (Study D0810C00019, Study PR-30-5011-C/NOVA) on non-g*BRCA*m patients treated with a polyadenosine 5'diphosphoribos polymerisation inhibitor, the median PFS ranged from 8 to 9 months compared to 4–5.5 months for those treated with placebo. Clinical trial simulations were performed assuming 250 patients enrolled over a 12-month period with 50% of patients enrolled after 8 months, a median PFS of 8.5 months and a piecewise exponential model for PFS. Across 500 simulations, it was estimated that the expected number of PFS events would be approximately 135 at 18 months (54% maturity) and

180 at 30 months (72% maturity), with a corresponding mean 95% confidence interval (CI) width of 3.87 and 3.27 months, respectively.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Four main analysis sets are defined for this study.

Full Analysis Sets:

Full Analysis Set (FAS). The FAS consists of all patients enrolled during the target enrolment period and assigned to olaparib. Patients are considered enrolled once it is confirmed that they meet all eligibility criteria (including non-g*BRCA*m status) and the request has been made by the Investigator for the provision of study treatment for that patient. Where a patient does not meet all the eligibility criteria but is enrolled in error she will still be a part of the FAS.

Safety Analysis Sets:

Safety Analysis Set (SAS). The SAS consists of all patients in the FAS who have received at least one dose of olaparib.

Patient-reported outcomes (PRO) Analysis Sets:

FACT-O Set. The FACT-O Set consists of all FAS patients with at least a baseline and a post-baseline assessment (excluding the end of treatment and 30-day follow-up assessments).

EQ-5D-5L Set. The EQ-5D-5L Set consists of all FAS patients with at least a baseline and a post-baseline assessment (excluding the end of treatment and 30-day follow-up assessments).

Table 1: Study Outcome Measures and Analysis Sets

Study Outcome Measures		**Analysis Set(s)**
Demographics and baseline characteristics		FAS
Important protocol deviations		FAS
Primary Outcome	PFS	FAS
	TFST	FAS

Study Outcome Measures		**Analysis Set(s)**
Secondary Outcomes	TDT	FAS
	PFS by HRD subgroups	FAS
	CT-FI	FAS
	OS	FAS
	FACT-O TOI score	FACT-O Set
Safety Outcomes	AE/SAE	SAS
	Clinical chemistry/hematology parameters	SAS
Exploratory Outcomes	PFS by molecular measures of HRR and genomic instability	FAS
	PFS and OS by TP53 disruption status	FAS
	FACT-O subscales and total score	FACT-O Set
	EQ-5D-5L index	EQ-5D-5L Set
	EQ-VAS score	EQ-5D-5L Set

2.2 Violations and deviations

The following general categories will be considered important protocol deviations and will be programmatically derived from the electronic case record form (eCRF) data. These will be listed and discussed in the clinical study report (CSR) as appropriate:

- Patients entered but who did not receive study treatment (Deviation 1).
- Patients who deviate from key entry criteria per the Clinical Study Protocol (inclusion criteria 3, 4, 5, 6, and 12, and exclusion criteria 4, 5, 8, 9, 11, 12, and 13) (Deviation 2).
- Baseline RECIST 1.1 scan > 42 days before first dose of study treatment (Deviation 3).
- No baseline RECIST 1.1 assessment on or before date of first dose of study treatment (Deviation 4).
- Received prohibited concomitant medications (including other anti-cancer agents) (Deviation 5). Please refer to the Clinical Study Protocol section 7.7 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.

The important protocol deviations will be listed and summarised using the FAS. Deviation 1 will lead to exclusion from the SAS. None of the other deviations will lead to patients being excluded from the analysis sets described in section 2.1.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST responses

Patients with measurable or non-measurable disease or no evidence of disease assessed at baseline by computed tomography (CT)/ magnetic resonance imaging (MRI) will be entered in this study. RECIST 1.1 (Eisenhauer et al, 2009) has been modified to allow for the assessment of progression due to new lesions in patients with no evidence of disease at baseline. For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to modified RECIST version 1.1. This tumor response data will also be used to determine if, and when, a patient has progressed in accordance with RECIST, and also to determine the patients' best overall response.

RECIST assessment should be performed no more than 28 days before the start of study treatment, and should be ideally performed as close as possible to the start of study treatment. Subsequent tumor assessments will be conducted every 8 weeks (±7 days) for the first 12 months and then every 12 weeks (± 7 days) until documented disease progression.

If an unscheduled assessment was performed and the patient had not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed, to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

At each visit, an overall visit response will be determined using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions. For the investigator assessments this will be done programmatically and the RECIST outcomes will be calculated using a computer program. Progression for patients with no evidence of disease at study enrollment will be assessed on the appearance of new lesions (see section 3.1.3 below).

3.1.1 Evaluation of target lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must

have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements. A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. The site and location of each TL should be documented as well as the LD for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters.

Note: For patients who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions. If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

For patients with no evidence of disease at baseline (i.e. no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at the baseline visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be no evidence of disease, unless progressive disease occurs due to presence of new lesions.

At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters:

At each visit the sum of TLs LD will be calculated as:

- Visit (i) total TLs diameter (mm) = Sum of visit (i) (TL1: TL5) LD;

Where (i) is any visit where the tumor assessment is performed.

The % change from baseline sum of TLs LD will be calculated as:

- % Change from baseline total TLs diameter = 100*(Visit (j) total TLs diameter (mm) – Baseline total TLs diameter)/(Baseline total TLs diameter);

Where (j) is any post-baseline visit where the tumor assessment is performed.

The previous smallest sum of total TLs diameter on study at visit (i) will be calculated as:

- Previous smallest total TLs diameter (mm) = min (Visit (1 to i-1) total TLs diameter);

This is to be repeated for each visit.

At each visit, the difference from the previous smallest sum of total TLs diameter will be calculated as:

- Change from previous smallest total TLs diameter (mm) = (Visit (i) total TLs diameter – previous smallest total TLs diameter at visit (i))

The % change from the previous smallest sum of total TLs diameter will be calculated (for each visit) only if the previous smallest total TLs diameter > 0 as:

- % Change from previous smallest total TLs diameter = 100*(Change from previous smallest total TLs diameter) / (Previous smallest total TLs diameter);

Table 2 provides the definitions of the criteria that are used to determine the objective tumor visit response for TLs.

Table 2: Target Lesion (TL) Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data:

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data:

For a visit to be evaluable then all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A NTL visit response of PD is recorded

- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Lymph nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL Visit responses subsequent to CR

A CR response can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.

- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD then response will be set to PD.

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up as described below as long as there remain ≤ 1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

- Step 3: If after both steps PD has not been assigned, then a scaled sum of diameters will be calculated (as long as ≤ 1/3 TLs have missing measurements), treating the lesion with intervention as missing, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0mm (or <10mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0mm recorded. If scaling up is not appropriate due to too few non-missing measurements then the visit response will be set to NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If ≤ 1/3 of the TL measurements are missing (because of an intervention) then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements).

Example of scaling

Lesion	**Longest diameter at nadir visit (cm)**	**Longest diameter at follow-up visit (cm)**
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 is missing at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of target lesions

CT, MRI and clinical examination are the only methods of assessment that can be used within the trial, with CT and MRI being the preferred methods and clinical examination only used in special cases (see study protocol for more information of tumor assessment of this study). If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.2 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record the overall response for NTLs at the investigational site at each visit.

Table 3: Non-Target Lesion (NTL) Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only, or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

3.1.3 New lesions

The presence of one or more new lesions is assessed as progression. A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

3.1.4 Overall response

The overall visit response will be derived using the algorithm shown in Table 4:

Table 4: Overall Visit Responses

TLs	NTLs	New Lesions	Overall Response
NA	NA	No	NED
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NA = not applicable, NE = not evaluable, NED = no evidence of disease.

3.2 Primary variable

3.2.1 Progression-free survival

PFS is defined as the time from the date of the first dose of olaparib, until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of progression), regardless of whether the patient withdraws from treatment or receives another anti-cancer therapy prior to progression (in months) and is calculated as follows:

- PFS (months): ((earliest of [date of progression; date of death] or date of censoring) – start date of olaparib + 1) / 30.4375.

Patients who have not progressed or died at the date of data cut-off (DCO), will be censored at the time of the latest date of tumor assessment according to modified RECIST v1.1.

However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable tumor assessment prior to the two missed visits. Two missed visits will equate to more than 18 weeks follow-up since the previous RECIST assessment occurred during the first 12 months, or more than 26 weeks follow-up if the last evaluable assessment occurred on or after the 'week-48' visit (allowing for visit windows). If the patient has no evaluable visits they will be censored at Day 1, unless they die within two visits (17 weeks allowing for visit window) from baseline.

The PFS time will always be derived based on scan/assessment dates, not visit dates. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Censored patients' follow-up time (months) will be calculated as follows:

- (date of censoring – start date of olaparib + 1) / 30.4375.

3.3 Secondary variables

3.3.1 Time to first subsequent therapy or death

TFST is defined as the time from the date of the first dose of olaparib to the earliest of the dates of death or commencement of first subsequent anticancer treatment.

- TFST (months): ((earliest of [date of death; start date of anticancer treatment post-baseline] or date of censoring) – start date of olaparib + 1) / 30.4375.

Patients who are alive and have not been recorded as taking a subsequent anticancer treatment, will be censored at the last date that the patient was known not to have received a first subsequent anti-cancer therapy i.e., these patients will be censored at the earliest of their last known to be alive and termination dates.

The subsequent anticancer therapies will be documented as follows:

- Therapy Class (Platinum Chemotherapy, Taxane Chemotherapy, PARP Inhibitor, Immunotherapy, Hormonal Therapy, Cytotoxic Chemotherapy, Targeted Therapy, Antiangiogenic Therapy, Radiopharmaceuticals, Other)
- Agent name (Anatomical Therapeutic Chemical [ATC] class and preferred name)

3.3.2 Time to treatment discontinuation or death

TDT is defined as the time from the date of the first dose olaparib to the earliest of the dates of death or discontinuation of olaparib.

- TDT (months): ((earliest of [date of death; date of discontinuation of olaparib] or date of censoring) – start date of olaparib + 1) / 30.4375.

Patients who are alive and are still receiving olaparib will be censored at the last recorded date they are known to be alive.

3.3.3 Progression-free survival by HRD subgroups

PFS as described in section 3.2.1 will be also performed in the following subgroups:

- HRD scar positive and/or s*BRCA* mutated;
- HRD scar positive, non-*BRCA* mutated;
- HRD scar negative, non-*BRCA* mutated.
- s*BRCA* mutated.

The Myriad myChoice HRD plus test will return HRD scar results as a numerical value and will identify patients with a deleterious or suspected deleterious mutation in tumor *BRCA* (t*BRCA*). An HRD score ≥42 will be considered as HRD scar positive. The Myriad BRCAnalysis CDx test will identify patients with a deleterious or suspected deleterious mutation in germline *BRCA* (g*BRCA*).

s*BRCA* mutated patients will be identified as those that have a deleterious or suspected deleterious mutation in t*BRCA* by the Myriad myChoice HRD plus assay and an absence of deleterious or suspected deleterious mutation in g*BRCA* by the Myriad BRCAnalysis CDx test. Non-*BRCA* mutated patients will be identified by having an absence of a deleterious or suspected deleterious mutation in both t*BRCA* and g*BRCA* as determined by the relevant test.

3.3.4 Chemotherapy-free interval

CT-FI is defined as the time from the date of the last dose of platinum chemotherapy in the course, immediately prior to enrolment in the study until the date of commencement of the first subsequent anticancer treatment (whether or not this is chemotherapy).

- CT-FI (months): ((start date of anticancer treatment post-baseline or date of censoring) – last dose date of platinum chemotherapy + 1) / 30.4375.

Patients who are alive and have not been recorded as taking a subsequent anticancer treatment, will be censored at the last date that the patient was known not to have received a first subsequent anti-cancer therapy i.e., these patients will be censored at the earliest of their last known to be alive and termination dates. Patients who have died prior to the start of a subsequent anticancer treatment will be censored at their date of death.

3.3.5 Overall survival

OS is defined as the time from the date of the first dose of olaparib to the date of death from any cause, with patients alive at the data cut-off date censored on the last recorded date on which the patient was known to be alive.

- OS (months): (date of death or date of censoring) – start date of olaparib + 1) / 30.4375.

For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE CRF page is only completed for patients off treatment if a survival sweep is not performed). The last date for each individual patient is defined as the latest among the following dates recorded on the CRFs:

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF

- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

3.3.6 Functional assessment of cancer therapy – ovarian (trial outcome index)

The secondary endpoint for HRQoL analysis will be the TOI score. The FACT-O is composed of the following subscales: physical, social/family, emotional, and functional well-being (FWB) as well as the additional concerns scales consisting of specific ovarian cancer symptoms (see Appendix G in Clinical Study Protocol). The TOI score will be derived from the sum of the scores of the 25 items included in the physical well-being (PWB) (7 items), FWB (7 items), and ovarian cancer subscale (OCS) (11 items) of the FACT-O questionnaire version 4. CCI [redacted]

For each patient the subscales and the TOI will be calculated as follows:

- Physical well-being (PWB):
  - If the number of available items n(PWB) is ≥ 4 then: PWB=7*[(4-gp1)+(4-gp2)+(4-gp3)+(4-gp4)+(4-gp5)+(4-gp6)+(4-gp7)] / n(PWB);
  - If n(PWB) is <4 then set PWB to missing.
- Functional well-being (FWB):
  - If the number of available items n(FWB) is ≥ 4 then: FWB=7*[gf1+ gf2+ gf3+ gf4+ gf5+ gf6+ gf7] / n(FWB);
  - If n(FWB) is <4 then set FWB to missing.
- Ovarian cancer subscale (OCS):
  - If the number of available items n(OCS) is ≥ 6 then: OCS= 11*[(4-o1)+(4-c2)+c3+(4-o2)+c6+c7+bmt5+b9+(4-o3)+bl4+(4-b5)] / n(OCS);
  - If n(OCS) is <6 then set OCS to missing.

Missing items will not concur to the calculation of the scores.

- TOI = PWB + FWB + OCS.

TOI absolute values and change from baseline will be calculated for each patient at each visit.

For each post-baseline visit a patient will be classified as in Table 5:

Table 5: Classification of TOI Change from Baseline

Category	TOI change from baseline
Improved	>0
Deteriorated*	≤ -10
No change	[-9; 0]

TOI = trial outcome index.

* If a patient has a baseline TOI <10, she will not be included in the denominator to evaluate the proportion of patients that have deteriorated.

3.4 Safety variables

Safety and tolerability will be assessed in terms of drug exposure, dose intensity, AEs, SAEs, adverse events of special interest (AESIs), other significant adverse events (OAEs), laboratory data (chemistry, hematology, and urinalysis), vital signs and the ECOG performance status.

3.4.1 Exposure

3.4.1.1 Drug exposure

The total treatment duration will be derived irrespective of treatment interruptions, by using the following formula:

- Total treatment exposure (months) = (last dose date - first dose date + 1) / 30.4375.

The actual treatment exposure is equal to the total treatment exposure, excluding dose interruptions and cases when the patient forgot to take a dose (this calculation does not take dose reductions into account).

The time on study will be derived using the following formula:

- Time on study (months) = (earliest (date last known to be alive, date of termination) – first dose date + 1) / 30.4375.

3.4.1.2 Dose intensity

Dose intensity will be derived by the following two standard definitions: relative dose intensity (RDI) and percentage intended dose (PID).

RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation, and will be derived by using the following formula:

- RDI = 100% * d/D

where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing, and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.

PID is the percentage of the actual dose delivered relative to the intended dose through progression and will be derived using the following formula:

- PID = 100% * d/D

where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

Examples of dose intensity calculations can be found in the Appendix (section 8.1).

3.4.2 Adverse events

AEs and SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period (30 days after discontinuing olaparib except for AESIs). Investigators will report during the regular follow-up for OS if the patient has developed an AESI of Myelodysplastic syndrome (MDS) or Acute myeloid leukemia (AML) or a new primary malignancy.

3.4.2.1 Adverse events of special interest

AESIs for olaparib are MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

A summary table will be produced capturing these toxicities of interest from first dose of olaparib until the end of the study (i.e. not restricted to treatment emergent AEs).

3.4.2.2 Other significant adverse events

An AstraZeneca medically qualified expert will review the list of AEs extracted from the database, and identify AEs of particular interest that were not reported as SAEs or AEs leading to discontinuation. Examples of these could be marked as hematological and other

laboratory abnormalities, and certain events that lead to an intervention (other than those already classified as serious), dose reduction or significant additional treatment. These AEs will be indicated by the AstraZeneca expert as OAEs. The list of OAEs will then be integrated in the derived datasets to report them separately.

3.4.3 Laboratory results

3.4.3.1 Clinical chemistry, hematology and urinalysis

Blood samples for the determination of clinical chemistry, hematology and urinalysis, will be taken at screening, baseline, visit 3 (Day 29), every 4 weeks thereafter during the first year of follow-up, every 12 weeks after 12 months follow-up, at study treatment discontinuation, and at follow-up 30 days after the last dose of the study treatment. Urine samples for the determination of urinalysis will be taken at screening, baseline and as clinically indicated thereafter.

The following variables of clinical chemistry, hematology and urinalysis will be analyzed in this study (Table 6).

Table 6: Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Absolute neutrophil count	S/P-Alkaline phosphatase (ALP)
B-Absolute lymphocyte count	S/P-Aspartate aminotransferase/transaminase (AST)
B-Platelet count	S/P-Alanine aminotransferase/transaminase (ALT)
B-Mean cell volume (MCV)	S/P-Albumin
	S/P-Calcium
	S/P-Potassium
Urinalysis (dipstick)	S/P-Sodium
U-Hb/Erythrocytes/Blood	S/P-Urea or Blood Urea Nitrogen (BUN)
U-Protein/Albumin	S/P-Total Protein
U-Glucose	

3.4.4 ECOG

ECOG (Oken M et al, 1982) performance status (see Table 7) is performed at screening, baseline, at the start of each tumor assessment visit (Visit 4 and thereafter every 8 weeks for the first 12 months, every 12 weeks thereafter) and at the treatment discontinuation visit.

Table 7: ECOG Performance Status

GRADE	ECOG performance status
0	Normal activity
1	Restricted activity
2	In bed less than or equal to 50% of the time
3	In bed more than 50% of the time
4	100% bedridden
5	Death

3.4.5 Vital signs

Weight, pulse, blood pressure (systolic and diastolic), and body temperature will be assessed at screening, baseline and as clinically indicated thereafter.

3.5 Exploratory variables

3.5.1 Progression-free survival by important characteristics

PFS as defined in section 3.2.1 of this SAP will be summarized according to subgroups based on important clinical characteristics, which will include Myriad myChoice HRD plus test parameters:

- HRR deleterious or suspected deleterious mutation (yes vs. no)
- Disruptive or non-disruptive mutation in TP53 (yes vs. no)

and data collected in the electronic case report form (eCRF):

- Best response to the last platinum regimen (CR or PR);
- Prior use of bevacizumab in combination with the penultimate platinum regimen;
- Number of prior platinum regimens (two vs. greater than two);
- Degree of sensitivity to the penultimate platinum chemotherapy: partial (6-12 months PFS) vs. fully (≥12 months PFS) sensitive;

  - Previous platinum chemotherapy PFS will be defined as the time from the date of the last dose of the penultimate platinum chemotherapy to the date of disease progression (in their penultimate platinum chemotherapy).

- Histological subtype (HGSOC vs. high grade endometrioid cancer).
  - Serous vs. endometrioid.
- Measurable disease vs. non-measurable disease vs. no evidence of disease at baseline
  - Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in LD (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI at the baseline visit.
  - Non-measurable disease is defined as patients with NTLs but no TLs at the baseline visit.
  - No disease at baseline is defined as no TLs and no NTLs at baseline.
- Age (years) at enrolment (<65 vs. >=65).

3.5.2 Overall survival by TP53 disruption status

- OS as defined in section 3.3.5 will be repeated by: Disruptive or non-disruptive mutation in TP53 (yes vs. no).

3.5.3 Functional assessment of cancer therapy – ovarian (subscales and total scores)

FACT-O subscale and total scores will be included in exploratory analyses, PWB (7 items), social/family well-being (SWB) (7 items), emotional well-being (EWB) (6 items), FWB (7 items), OCS (11 items). FACT-O total score (all 38 items), PRO-deterioration free (10-point TOI deterioration) survival will also be explored.

For PWB, FWB and OCS subscales' scoring refer to section 3.3.6. The other scores will be calculated as follows:

- Social/family well-being (SWB):
  - If the number of available items n(SWB) is >=4 then:
    SWB =7*[gs1+gs2+gs3+gs4+gs5+gs6+gs7] / n(SWB);
  - If n(SWB) is <4 then set SWB to missing.
- Emotional well-being (EWB):
  - If the number of available items n(EWB) is >=3 then:
    EWB=6*[(4-ge1)+ge2+(4-ge3)+(4-ge4)+(4-ge5)+(4-ge6)] / n(EWB);

- If n(EWB) is <3 then set EWB to missing.

Missing items will not concur to the calculation of the scores.

- FACT-O total score = PWB + FWB + OCS + SWB + EWB.

PRO-deterioration free survival is defined as the time from the date of first dose of olaparib, until the earliest date a patient became 'deteriorated' as described in section 3.3.6.

- PRO-deterioration (months): (earliest of [date of deterioration; date of death] or date of censoring – start date of olaparib + 1) / 30.4375.

Patients who have not been classified as 'deteriorated' until the time of analysis will be censored at the time of the latest date of FACT-O assessment.

3.5.4 Plasma and red cell folate, and plasma B12

It is possible that the macrocytic anaemia associated with olaparib administration in a proportion of patients is associated with reduced folate or B12 levels. To investigate whether levels are reduced during maintenance treatment with olaparib, plasma and red cell folate levels, and plasma B12 levels will be measured at baseline/Visit 2 and at the end of treatment/treatment discontinuation visit. Samples will be analyzed at a central laboratory. These analyses are outside of the scope of this SAP and will not be included in the CSR. These analyses will be described and reported elsewhere.

3.5.5 EuroQol five dimensions, five levels

The EQ-5D questionnaire is made up of two components; health state description and evaluation. In the description part, health status is measured in terms of five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients will self-rate their level of severity for each dimension using a five-level scale. In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS) (see Appendix H in Clinical Study Protocol).

EQ-5D index and the EQ-VAS score including the change from baseline for both scores will be summarized. The EQ-5D-5L profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population. Where a valuation set has not been published, the

EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (van Hout et al 2012). The EQ-VAS will be reported separately.

3.5.6 Correlation between HRD status and ctDNA

Biomarker analysis: Correlation between HRD score and ctDNA levels.

ctDNA levels will be assessed at screening and treatment discontinuation visits. The HRD score will be performed using the Myriad's myChoice HRD plus test. These analyses are outside of the scope of this SAP and will not be included in the CSR. These analyses will be described and reported elsewhere.

4. ANALYSIS METHODS

Statistical analysis and generation of all tables, listings and figures will be performed using SAS® (SAS Institute, North Carolina), version 9.4 or higher.

4.1 General principles

Patients' listings of key data represented in the eCRF will be provided. Measurements from patients excluded from the pre-defined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the patient listings. This is not applicable for unscheduled tumor assessments that will be considered for PFS evaluation. In general, the patient listings will be sorted by patient number and assessment date (and time), if applicable.

4.1.1 Baseline definition

Baseline is defined to be the last evaluable measurement prior to starting treatment. Change from baseline will be derived for each visit where there is available data.

4.1.2 General descriptive statistics

Categorical variables will be summarized as frequency counts and percentages (%) of patients in each category. As general rules, descriptive statistics will be drawn on patients with available data. Counts of missing data will be provided in all tables for information only. Percentages will be rounded up to one decimal place.

Continuous variables will be presented as the number of observations (n), mean, standard deviation, median, first and third quartiles (Q1 and Q3; presented only for selected variables), minimum and maximum. The same number of decimal places as in the raw data will be

presented when reporting minimum and maximum, one more decimal place than in the raw data will be presented when reporting mean, median, Q1 and Q3, and two more decimal places than in the raw data will be presented when reporting standard deviation.

4.1.3 Rules for handling missing data

Every effort will be made to capture all available data. Unless explicitly stated otherwise, missing data will not be imputed and data will be analyzed and presented as they are recorded in the database. The extent of missing data will be indicated for all variables in descriptive tables.

The below partially missing dates will be imputed as per the phUSE guidelines. Imputation rule is assuming the worst / make the most conservative judgment when imputing AE and CM start/stop dates. Duration of AE/CM should not be derived using imputed dates. The purpose of imputing a start date is to help define whether the AE/CM started while taking the study drug.

For missing start date:

- Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug, then impute first dose date.
- Missing day and month – impute 1st January unless year is the same as first dose date, then impute first dose date.
- Completely missing – impute first dose date unless the end date suggests it could have started prior to this, in which case impute the 1st January of the same year as the end date.
- When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or CM.

For missing stop date:

- Missing day - Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date. If last dose date occurs in a subsequent month then the last day of the month imputation will be kept.
- Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.

- Completely missing – need to look at whether the AE/CM is still ongoing before imputing a date and also when it started in relation to study drug. For CM if the ongoing flag is marked or the ongoing flag is missing then assume that the CM is still being taken (i.e. do not impute a date). If the AE/CM has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after the first dose date, then impute the last dose date.

When dates and times are imputed, a flag should be provided to show that this is an imputed rather than actual date. The Clinical Data Interchange Standards Consortium Analysis Data Model has some rules to follow for both date and time imputations. Date imputation flags should have the name suffix –DTF and contain "D" for day, "M" for month, or "Y" for year. Note that "M" implies that both the day and month are imputed, and "Y" implies day, month, and year are all imputed.

4.1.4 Data cut-off

1. The DCO for the interim analysis will be approximately 18 months after the first patient is enrolled, when approximately 135 PFS events have occurred. Additional follow-up data will be collected after the DCO for the primary analysis approximately 30 months after first patient is enrolled (a minimum period of 18 months from last patient is enrolled), when approximately 180 PFS events have occurred. A supplementary analysis of OS is expected when approximately 135 death events have occurred, estimated to be approximately 36 months after the first patient is enrolled.
2. Survival calls will be performed in the week following the date of DCO for the primary PFS analysis and supplementary analysis of OS, and if patients are confirmed to be alive or if the death date is past the DCO date these patients will be censored at the date of DCO.

   The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the primary PFS analysis (and final supplementary OS analysis) should be obtained by site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent for the processing of their

personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3. PRO questionnaires (FACT-O and EQ-5D-5L) will be collected from the patient at baseline, at day 29, at day 57 and every 8 weeks for the first 12 months, then every 12 weeks (+/- 7 days), at study treatment discontinuation visit and at follow-up 30 days after the last dose of the study treatment.

4.1.5 Visit windows

Due to the practicality of scheduling patient visits, not all patients will have visits on the same study day. To allow for any presentations that summarize values by visit, visit windows will be defined according to Table 8. The upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). The half way point is assumed to be the midpoint of the number of days between the visits, excluding both visit days (for example there are assumed to be 56 days between Day 56 and Day 112). If an odd number of days exist between two consecutive visits then the upper limit is taken as the midpoint value plus 0.5 day.

Table 8: Visit Windows

Visit	Day	Safety assessments (Laboratory)	ECOG/Tumor assessments	Questionnaire assessments
		Visit window (min : max)		
Screening	Up to Day 1	(-28 : -1)		
Day 1, Baseline	Day 1	(1 : 1)		
Day 29	Day 29	(2 : 43)		(2 : 43)
Week 8	Day 56	(44 : 70)	(2 : 84)	(44 : 98)
Week 12	Day 84	(71 : 98)		
Week 16	Day 112	(99 : 126)	(85 : 140)	(99 : 140)
Week 20	Day 140	(127 : 154)		
Week 24	Day 168	(155 : 182)	(141 : 196)	
Week 28	Day 196	(183 : 210)		
Week 32	Day 224	(211 : 238)	(197 : 252)	
Week 36	Day 252	(239 : 266)		
Week 40	Day 280	(267 : 294)	(253 : 308)	
Week 44	Day 308	(295 : 322)		
Week 48	Day 336	(323 : 350)	(309 : 378)	
Week 52	Day 364	(351 : 392)		
Week 60	Day 420	(393 : 462)	(379 : 462)	
Week 72	Day 504	(463 : 546)		
Week 84	Day 588	(547 : 630)		
Week 96	Day 672	(631 : 700)		
Week 104	Day 728	(701 : 756)		

In addition, an End of Treatment visit will be identified as the visit occurring between 1 and 8 days (inclusive) after the end of treatment. Similarly, a 30-day follow-up visit will be identified as the visit between 9 and 31 days (inclusive) following end of treatment. These additional points will allow summaries to be presented for these post-treatment visits. Values mapped both to scheduled and post-treatment visits will be assigned to both as per visit windows definition.

If there is more than one value per patient within a time window then the closest value will be summarized, or the earlier value in the event the values are equidistant from the nominal visit day. For the End of Treatment and 30-day follow-up visits the earlier value will be summarized in case there is more than one per patient. In case of multiple assessments within the same time window, if the closest/earlier assessment has missing values for one or more parameters then the missing records will be derived by the subsequent farther/later assessment.

Analysis visits will be determined based upon assessments dates and not on nominal visits designated in the database.

4.2 Analysis methods

4.2.1 Baseline descriptive analysis

All baseline descriptive analyses except 'patients disposition' based on enrolled patients will be based on the FAS.

4.2.1.1 Patient disposition

The following frequencies (number and percent) will be displayed for all patients.

- Patients screened
  - Patients with screen failure and excluded from the study
  - Patients enrolled in the study.
    - Patients included in the FAS
    - Patients included in the SAS
    - Patients included in the FACT-O Set
    - Patients included in the EQ-5D-5L Set
    - Patients ongoing in the study
    - Patients discontinued from the study (and reasons)
    - Patients ongoing study treatment
    - Patients who discontinued the treatment (and reasons)

The denominators for the percent calculations will be the number of patients enrolled in the study i.e. number of patients entered (including those who did not receive treatment but excludes screening failures), whether or not they are included in any of the analyses.

4.2.1.2 Protocol deviations

A listing of important protocol deviations will be provided for all patients. The number of patients with at least one important protocol deviation and the corresponding count and percentage of patients in each important protocol deviation category will be summarized.

4.2.1.3 Demographics and baseline characteristics

Demographics and baseline characteristics will be listed and summarized for all patients in the FAS. Demographic characteristics include age, age group, race, ethnicity and country. Patient

baseline characteristics include heart rate (pulse), systolic and diastolic blood pressure, weight and body temperature.

Age group is divided into four categories, i.e. <50, ≥50 - < 65, ≥ 65 - <75 and ≥ 75.

Weight group is divided into three categories, i.e. < 70, ≥ 70 - ≤ 90, > 90.

Baseline characteristics will also include:

- General pathology characteristics at baseline, including Time from original diagnosis (years), primary tumor location, Federation of Gynecology and Obstetrics tumor stage, histology type, platinum sensitivity to the penultimate platinum chemotherapy, objective response to latest platinum-chemotherapy and overall disease classification.
- Time from original diagnosis (years) = (date of informed consent – date of original diagnosis + 1) / 365.25.
- BRCA testing performed at screening: local (blood, saliva/scraping or tumor) test or central (blood) test; absence of deleterious or suspected deleterious BRCA mutation (yes, no, unknown).
- Tumor and blood central /Myriad tests: g*BRCA* status (*BRCA1*, *BRCA2*, both, negative, unknown); t*BRCA* status (*BRCA1*, *BRCA2*, both, negative, unknown), s*BRCA* status (positive, negative, unknown), HRD status (positive, negative, unknown), HRR mutation status (positive, negative, unknown), disruptive or non-disruptive mutation TP53 mutation status according to t*BRCA* status (yes, no, unknown).
- ECOG performance status at baseline (see Table 7 of section 3.4.4).
- The extent of the disease at baseline (locally advanced or metastatic) and the corresponding sites.

The frequency and % of the above baseline characteristics will be calculated. The descriptive summaries will be provided for time from original diagnosis (years).

Categories will be summarized as they are collected in the eCRF.

4.2.2 Medical/surgical history and blood transfusion

Medical and surgical history will be coded using the latest available version of MedDRA coding dictionary. The version of the coding dictionary used will be included in a footnote on

the output. Coded medical history terms will be summarized for the FAS, by MedDRA System Organ Class (SOC) and PT. SOC terms will be sorted alphabetically and then PTs will be sorted in order of frequency.

Patient listings of coded medical and surgical history terms will be provided for the FAS.

Blood products transfusions' details (product type, units, volume, transfusion origin and date) will be listed for the FAS.

4.2.3 Medication and prior cancer therapy/radiotherapy

A summary of the prior and CM received, prior cancer therapy and prior radiotherapy will be provided for the FAS. Medications (prior, concomitant) will be coded using the latest available version of World Health Organization Drug Dictionary (WHODrug). The WHODrug version used will be specified in the data display footnote. Prior and CMs will be presented in the same table and sorted alphabetically by ATC class (and preferred drug name).

In addition a summary of previous disease-related treatment modalities (Platinum Chemotherapy, Taxane Chemotherapy, PARP Inhibitor, Immunotherapy, Hormonal Therapy, Cytotoxic Chemotherapy, Targeted Therapy, Antiangiogenic Therapy, Radiopharmaceuticals, Other). The count (%) of patients by number of previous platinum chemotherapy regimens received will be also presented. The summary of the number of previous regimens will be reported as well. Previous disease related-related chemotherapy treatments will also be presented by regimen order.

All medications will be also listed for the FAS.

4.2.4 Primary variable

PFS as defined in section 3.2.1 will be summarized using the total number and % of patients experiencing a PFS event and the type of event (RECIST progression or death in absence of progression). The number and % of censored patients will be presented including patients progression-free at the time of the analysis or discontinued the study.

In addition, the PFS rate and associated 95% CI will be summarized at six-monthly intervals using the Kaplan-Meier (KM) method, the median PFS and corresponding 95% CI (whenever estimable) and the median follow-up time in censored patients (in months) will be also included.

PFS will be also presented in a KM graph that will include tick marks to identify censored observations and number at risk at baseline and at three-monthly intervals. The primary analysis will be based on the FAS.

4.2.4.1 Sensitivity analyses of the primary variable

A sensitivity analysis may be performed on PFS excluding any patients from the FAS who did not have a negative g*BRCA*m status confirmed by the central Myriad test.

Attrition bias will be assessed by repeating the PFS analysis using the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumor assessments. In addition, and within the same sensitivity analysis, patients who take subsequent therapy prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

A 'deviation bias' sensitivity analysis may be performed on PFS excluding patients with important protocol deviations that may affect the efficacy of the trial therapy. The need for such a sensitivity analysis will be determined following review of the important protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

4.2.5 Secondary variables

All the secondary analyses except PRO outcomes will be based on the FAS.

4.2.5.1 Time to first subsequent therapy or death

TFST as defined in section 3.3.1 will be summarized in the same way as PFS as described in section 4.2.4.. The number and % of patients commencing subsequent anticancer treatment or died in the absence of subsequent anticancer treatment will be presented. The number and % of censored patients will be presented including patients who have not commenced subsequent anticancer treatment at time of the analysis or discontinued the study.

The number and % of patients with any subsequent anticancer therapies and therapy class and agent names (coded as ATC) will be summarized.

4.2.5.2 Time to study treatment discontinuation or death

TDT as defined in section 3.3.2 will be summarized in the same way as PFS as described in section 4.2.4. The number and % of patients who have discontinued treatment or died in the

absence of treatment discontinuation will be presented. The number and % of censored patients will be presented, these being patients who are still on treatment at the time of the analysis.

4.2.5.3 Progression-free survival by HRD subgroups

PFS will be summarized in the same way as PFS as described in section 4.2.4 in the following subgroups as defined in section 3.3.3:

- HRD scar positive and/or s*BRCA* mutated;
- HRD scar positive, non-*BRCA* mutated;
- HRD scar negative, non-*BRCA* mutated;
- s*BRCA* mutated.

Overlaid KM curves will be provided.

4.2.5.4 Chemotherapy-free interval

CT-FI as defined in section 3.3.4 will be summarized in the same way as PFS as described in section 4.2.4. The number and % of patients who have commenced subsequent anticancer treatment will be presented. The number and % of censored patients will be presented including patients who have not commenced subsequent anticancer treatment at time of the analysis, discontinued the study or died prior to the start of a subsequent anticancer treatment.

4.2.5.5 Overall survival

OS as defined in section 3.3.5 will be summarized in the same way as PFS as described in section 4.2.4. The number and % of patients who have died will be presented. The number and % of censored patients will be presented, these being patients who are still alive at the time of the analysis and those who discontinued the study prior to death.

4.2.5.6 Functional assessment of cancer therapy – ovarian

Compliance

Summary measures of overall compliance and compliance over time will be derived for the FACT-O questionnaire. These will be based upon:

- Received forms = number of FACT-O forms received back plus the number not received back where the reason was patient ‘Too Affected by Symptoms of Disease Under Investigation’.

- Expected forms = number of patients still under HRQoL follow-up at the specified assessment time. For patients that have progressed, the latest of progression and safety follow-up will be used to assess whether the patient is still under HRQoL follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms.
- Evaluable forms = subset of expected FACT-O forms with at least one subscale that can be determined; or where the reason the patient did not complete the form was 'Too Affected by Symptoms of Disease Under Investigation'.

Thus the overall compliance rate is defined as the number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline FACT-O form.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

FACT-O trial outcome index

The proportion of patients with any improvement from baseline in TOI score and the proportion of patients with at least a 10-point deterioration from baseline in TOI score (see definitions in section 3.3.6) will be estimated together with the exact 95% CI (i.e., Clopper-Pearson CI).

The TOI index score and the change from baseline will be summarized using descriptive statistics and presented for each follow-up time point including data post progression, where available.

FACT-O TOI score will be also analyzed with a repeated measures analysis model.

Change from baseline in TOI score will be analyzed using a mixed model for repeated measures (MMRM) analysis for each visit. The analysis will evaluate the visit effect from baseline to the last assessment (which will include visit data obtained at baseline, day 29

[week 4], weeks 8, 16, 24, 32, 40, 48, 60, 72, 84, 96, and 104. The treatment discontinuation and follow-up visits will not be included in the model.).

The MMRM model will include patient and visit as explanatory variables, the baseline TOI score as a covariate along with the baseline TOI score by visit interaction. Visit will be the fixed effect in the model; patient will be included as a random effect. Restricted maximum likelihood (REML) estimation will be used. For each visit, the adjusted (least squares) mean estimates, corresponding 95% CIs, estimates of the visit difference, corresponding 95% CIs will be presented.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

```
proc mixed data=TOI method = reml;
  class VISIT SUBJECT;
  model TOISC = VISIT TOIBL TOIBL*VISIT / s ddfm=kr;
  repeated VISIT / type=UN subject=SUBJECT;
  lsmeans VISIT / at means pdiff diff alpha=0.05 cl;
```

where VISIT is the visit, TOISC is the change from baseline in the TOI score, and TOIBL is the baseline TOI score.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. If there are still issues with the fit of the model or estimation of the effects, SUBJECT will be treated as a fixed effect.

4.2.6 Exploratory variables

All the exploratory analyses except PRO outcomes will be based on the FAS.

4.2.6.1 Progression-free survival by important clinical characteristics

Similar analyses will be performed as in section 4.2.4 for subgroups as defined in section 3.5.1.

4.2.6.2 Overall survival by TP53 disruption status

Similar analyses will be performed as in section 4.2.5.5 for subgroups as defined in section 3.5.2.

4.2.6.3 Functional assessment of cancer therapy – ovarian

FACT-O total, PWB, FWB, OCS, SWB and EWB as described in sections 3.5.3 and 3.3.6 absolute scores and change from baseline will be summarized using descriptive statistics and presented for each visit including data post progression, where available.

4.2.6.4 EuroQol five dimensions, five levels

Summary measures of overall compliance and compliance over time will be derived for the EQ-5D-5L questionnaire using the same calculation described for the calculation of FACT-O compliance in section 4.2.5.6.

The EQ-5D index and EQ-VAS absolute scores and change from baseline will be summarized using descriptive statistics and presented for each visit including data post progression, where available (excluding discontinuation and follow-up visits that will be only listed).

The EQ-5D index and EQ-VAS will be also analyzed with repeated measures analyses model as described in section 4.2.5.6 for the FACT-O TOI.

Graphical plots of the mean EQ-5D index and EQ-VAS absolute scores and change from baseline with associated 95% CI by scheduled visits will be produced.

4.2.7 Safety variables

Safety and tolerability will be assessed in terms of drug exposure (see section 3.4.1), AEs, SAEs, AESIs and OAEs (see section 3.4.2), deaths (see section 6.3.12 of Clinical Study Protocol) and laboratory data (see section3.4.3), based on the SAS.

4.2.7.1 Drug exposure

Duration of drug exposure (total and actual), time on study and dose intensity (RDI and PID) will be summarized using descriptive statistics (number of valid observations, mean, standard deviation, median, Q1, Q3, minimum and maximum). Cumulative sum will be presented for drug exposure and time on study only.

In addition, the total number and % of patients with:

- Any dose reduction / interruption / modification (i.e. either dose reduction and/or interruption);
- 1 dose reduction / interruption / modification (i.e. either dose reduction and/or interruption);

- 2+ dose reductions / interruptions / modification (i.e. either dose reduction and/or interruption).

The reasons for dose reduction, interruption and modification will also be included.

4.2.7.2 Adverse events

The term AE is used to include both serious and non-serious AEs. AEs (both in terms of the MedDRA PTs and CTCAE grade) will be listed individually by patient and described by SOC and PT. Any AE occurring before treatment with olaparib will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 30 days of discontinuation of olaparib will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of olaparib) will be flagged in the data listings. All AEs and separately all AEs with outcome of death, all SAEs, all AEs leading to olaparib discontinuation will be tabulated by MedDRA SOC and PT. SOC terms will be sorted by international order and then PT will be sorted in order of frequency within each SOC. In the summary tables, patients may be counted under multiple SOCs and PTs, but for each SOC and PT, patients are only counted once. If a patient experiences the same AE more than once (based on MedDRA PT), the highest severity recorded based on CTCAE grade for the event will be presented.

Two tables will summarize the following categories of AEs using (i) number and % of patients and (ii) number of events:

- Any AE
- Any AE by maximum reported CTCAE grade
- Any AE causally related to study medication*
- Any AE by maximum reported CTCAE grade 3 or higher
- Any AE by maximum reported CTCAE grade 3 or higher causally related to study medication*
- Any AE with outcome of death
- Any AE with outcome of death causally related to study medication*
- Any SAE (including events with outcome of death)

- Any SAE (including events with outcome of death) causally related to study medication*
- Any AE leading to olaparib discontinuation
- Any AE leading to olaparib discontinuation causally related to study medication*
- Any AE leading to olaparib interruption
- Any AE leading to olaparib interruption causally related to study medication*
- Any AE leading to olaparib reduction
- Any AE leading to olaparib reduction causally related to study medication*
- Any AE leading to olaparib modification
- Any AE leading to olaparib modification causally related to study medication*

* as assessed by the investigator.

Summary tables will also be produced for the following common olaparib AEs, based on grouped preferred terms:

- Anaemia
- Neutropenia
- Thrombocytopenia
- Nausea
- Vomiting
- Fatigue/Asthenia

All the AEs will be also listed by patient including: verbatim term, SOC, PT, AE start-stop dates, relative AE start day, AE occurred after receipt of further therapy for cancer (following discontinuation of olaparib), maximum CTCAE grade, SAE (Y/N), action taken with regard to olaparib, AE caused by olaparib, AE caused patient´s withdrawal from study (Y/N), outcome.

4.2.7.3 Laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be taken at the times indicated in Table 1 and Table 2 of the Clinical Study Protocol, section 4.

All laboratory results and change from baseline in hematology and clinical chemistry will be summarized using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, min and max) and presented by visit.

A shift table will be produced showing the number and % of patients switching from normal, abnormal and not done laboratory results at baseline (the last lab result obtained prior to the start of olaparib treatment) to the minimum and maximum value on treatment (classified as normal, abnormal and not done).

For the evaluation of Hy's law, a table will be produced showing the number of patients with maximum on-treatment alanine aminotransferase/transaminase (ALT) and aspartate aminotransferase/transaminase (AST) values greater than 3, 5 and 10 times the upper limit of normal (ULN) the local laboratory reference ranges.
This summary will be produced overall and also split by maximum total bilirubin (TBL) values greater than 2 times the upper limit of the local laboratory reference range.

A plot of ALT vs. TBL values will also be produced with reference lines at 3×ULN for ALT, and 2×ULN for TBL. A plot of AST vs. TBL values will also be produced with reference lines at 3×ULN for AST, and 2×ULN for TBL. In each plot, TBL will be in the vertical axis.
Urinalysis results will be listed only.
The complete clinical laboratory measurements will be listed by patient and date.

4.2.7.4 Vital signs

Vital signs parameter values (weight, systolic blood pressure, diastolic blood pressure, pulse and body temperature) will be obtained at screening, baseline and clinically indicated thereafter (the date of collection and measurement will be recorded on the appropriate eCRF). As vital signs data are not collected at scheduled time points, these data will only be presented in a listing.

4.2.7.5 ECOG performance status

The ECOG performance status will be summarized at baseline and by visit using frequency and %s for each category. The ECOG performance status shift table by visit will be provided as increased/worsened (change from baseline > 0), decreased/improved (change from baseline

< 0) and no change (change from baseline = 0) and the related frequency and % will be summarized.

The complete ECOG performance status will be listed by patient and date.

5. INTERIM ANALYSES

An interim analysis of PFS will be performed approximately 18 months after the first patient is enrolled into the study. Based upon simulations (see section 8.2 in Clinical Study Protocol) it is estimated that approximately 135 events will have occurred at the time of the interim analysis, equating to approximately 54% data maturity. The primary focus of the interim analysis will be the primary and secondary endpoints and PFS by HRD status, the descriptive baseline characteristics and safety analyses.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The secondary objective concerning PFS according to tumor HRD status using the Myriad myChoice plus HRD test has been updated to include the following subgroups; (i) s*BRCA* mutated and/or HRD scar positive, (ii) HRD scar positive, non-*BRCA* mutated, (iii) HRD scar negative, non-*BRCA* mutated, and (iv) s*BRCA* mutated.

The exploratory objective concerning PFS stratified into a range of molecular sub-groups including MSI status and tumor mutation load score will not be performed.

7. REFERENCES

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

van Hout, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15.

8. APPENDICES

8.1 Examples of dose intensity calculations

The planned dosing schedule was 300 mg twice daily (a total daily dose of 600 mg per day).

Table 9: Example of Olaparib Dosing

RDI	PID	Patient	Study Day										
			1	2	3	4	5	6	7	8	9	10	11
100%	100%	1											P
100%	50%	2						D					P
50%	50%	3											P
77%	77%	4											P
62%	43%	5								D			P
	Received the total daily dose of 600 mg												
	Dose reduction (less than 600 mg; in this example 400 mg)												
	Missed dose (0 mg)												
D	Discontinuation of olaparib												
P	Progression (or censoring event)												

RDI: relative dose intensity; PID: percentage intended dose.

Patients 1-5 progressed on Day 11, so the intended dose through to progression was 10 * 600 mg of olaparib = 6000 mg.

Patient 1 received a total dose of 6000 mg of olaparib, whereas patients 2-5 received less treatment due to:

- Early stopping (Patient 2)
- Missed dose (Patient 3)
- Dose reduction and missed dose (Patient 4)
- Early stopping, missed doses and dose reductions (Patient 5)

Patient 1: RDI = PID = (10 * 600 mg)/ 6000 mg = 100%

Patient 2: RDI = (5 * 600 mg)/ 3000 mg = 100%

PID = (5 * 600 mg)/ 6000 mg = 50%

Patient 3: RDI = PID = (5 * 600 mg)/ 6000 mg = 50%

Patient 4: RDI = PID = ((5 * 600 mg) + (4 * 400 mg))/ 6000 mg = 77%

Patient 5: RDI = ((3 * 600 mg) + (2 * 400 mg))/ 4200 mg = 62%

PID = ((3 * 600 mg) + (2 * 400 mg))/ 6000 mg = 43%

CCI

[redacted]

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]